REMARKS

Claims 1-6, 13-15, 20-21, 26 – 35, are now pending in the application. The amendments are fully supported by the claims as filed and no new matter is believed to have been added.

The Examiner maintained her rejection of claims 13 – 14 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner maintained her rejection of claims 1-6, 13-15, 20-21 and 26 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 1-3 and 13-14 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al., (1996, J. Allergy Clin. Immun. Vol. 97(3):781-787).

The above amendments and the following remarks have addressed all the grounds for rejection and/or objection or have otherwise rendered them moot. Applicants respectfully request the Examiner reconsider all outstanding rejections, and that they be withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph – Claims 13-14

The Examiner maintained her rejection of claims 13 – 14 under 35 U.S.C. § 112, first paragraph, as allegedly still failing to comply with the written description requirement. The Examiner asserts that the specification and claims lack sufficient written description of the polynucleotide encoding the hybrid polypeptide. Applicants argued that the polynucleotide and polypeptide sequences for timothy grass pollen allergens were available in the art. The Examiner countered that the claims as originally presented encompassed fragments thereof wherein each fragment consists of at least eight consecutive amino acids from the respective allergenic proteins and that there was no

description of the fragments of nucleic acids that must encode the hybrid polypeptide. Basically, it was the Examiner's contention that the Applicants did not have possession of fragments of allergenic protein as at the filing of the instant Application. Applicants respectfully disagree and will address that issue in a separate section below.

Meanwhile, amended claim 1, from which claim 13 and 14 depend do not relate to fragments of allergenic proteins. Accordingly, this ground for rejection is now moot in regards to claims 13 and 14 and should be respectfully withdrawn. As regards new claims 30 and 31, and 34 and 35, relating to hybrid polypeptides comprising modifications and fragments of allergenic proteins prepared from the corresponding polynucleotides, Applicants will now show that they had possession of that subject matter as at the filing date of the instant Application.

There is Adequate Written Description for Modifications and Fragments of Plant Allergenic Proteins of the Present Invention

Applicants appreciate the basis of the Examiner's arguments particularly in view of PTO's Guidelines for Examination of Patent Application under the Written Description Requirement in which Examiners in the Biotechnology Unit are instructed not to issue claims to inventions for which the patent application does not describe the molecule by sufficient, relevant, identifying characteristics (as opposed to just functionality),however, the inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact.

Because the touchstone in 112, first paragraph jurisprudence is whether, from the perspective of one skilled in the art, the Applicant was in possession of the claimed material at the time of filing, and particularly, in order to appreciate the correlation between structure and function in this case, it is necessary that the Applicants and the Examiner share a common understanding of what the Applicants claim to be their invention.

This invention relates to rational allergen-specific immunotherapy based upon the Applicants' surprising discovery that hybrid allergens comprising epitopes of immunologically distinct allergens can be used for Type I allergy immunotherapy. Page 2,¶ 2. Being used for Type I allergy immunotherapy implies by definition that they elicit allergenic responses substantially reduced from those of the wild-type allergens from which they are derived. Therefore, to the extent that specific allergens have been isolated and sequenced, this invention teaches and claims a hybrid polypeptide comprising those isolated allergens, their modifications or fragments that can be used for allergen-specific immunotherapy provided the hybrid polypeptide induces protective antibody response. This invention encompasses hybrid polypeptides of all modifications by whatever means known in the art or all fragments having at least eight consecutive amino acids generated by whatever means known in the art which induce protective antibody response. The correlation between structure and function lie in the said induction of protective antibody response and the Applicants will now elaborate.

The conventional allergen-specific immunotherapy for Type I allergic reactions consists of pre-sensitization of the patient with allergen extracts.

A more rational approach, and to which a lot of research effort has been devoted in the art involves isolation of the specific allergenic proteins, followed by structural characterization of those isolated allergenic proteins, then followed by experimentally intensive mapping of IgE epitopic sites on the isolated allergenic proteins, and further carrying out site directed modifications of those characterized proteins in order to identify such modifications thereof that have reduced allergenicity compared to the native protein and yet capable of inducing allergen-specific desensitization for a patient who thereafter encounters the wild-type allergen. The Examiner can imagine the degree of experimentation necessary to carry out this rational approach to identifying therapeutic proteins for Type I allergy immunotherapy.

What the Applicants are claiming is a product generated by an equally rational but by far less experimentally intensive methodology based on the concept of protective antibodies. As the Examiner knows, immune reactions in Type I hypersensitivity are triggered by a cascade of biochemical responses initiated by the binding of IgE to the epitopic sites of the allergen. Protective or blocking antibodies, by definition, are those

that block or prevent the binding of IgE to the allergen. In essence, what Applicants have done is select as candidate therapeutic agents, hybrids of those isolated allergens, including modifications or fragments thereof capable of inducing blocking antibodies in vivo.

No one prior to the Applicants have taught that hybrid polypeptides comprised of known allergens or their modifications or fragments thereof can be used for Type I allergy immunotherapy. Further, Applicants disclosed, for lack of a better word, a heuristics methodology, based on the concept of blocking antibodies, that bypasses the need for extensive base by base or amino acid by amino acid structural characterization of allergens in order to rationally design them as immunotherapeutic agents.

The invention does not concern itself with the detailed structural profile of the hybrid allergens so long as the functional characteristics claimed to be of therapeutic interest is met. Clearly, the means of modifying or fragmenting proteins are old and well-known in the art and the law does not require that the instant specification be burdened by those well known details. However, any modification or fragment of a plant allergen comprising at least eight consecutive amino acids of the native protein falls within the ambit of this invention provided that the modifications or fragments can induce blocking or protective antibodies in vivo while at the same time eliciting tolerably low to none existent allergic reactions. In order to induce blocking or protective antibodies (IgG's), it is presumed necessary that those modifications or fragments contain IgG epitopic sites. But even at that, this invention does not concern itself with specific IgG epitopic mapping of candidate allergens, the invention teaches that at least eight consecutive amino acids of the native protein must be intact provided that when administered in vivo, the modification or fragment can induce blocking antibodies while eliciting tolerably low to none existent allergic reactions. Because a reasonable artisan will not have any doubt as to what the inventors possessed at the time of the invention in regards to fragments and modifications of hybrid allergenic polypeptides, it is asserted that the written description requirement has been met.

Now pointing to specific teachings in the Application, regarding fragments, the invention discloses that:

The invention therefore relates to a hybrid polypeptide comprising at least two different allergenic proteins or fragments thereof wherein each fragment consists of at least eight consecutive amino acids of the respective allergenic protein. Page 2, ¶ 2.

[T]he hybrid polypeptide comprises at least one fragment of an allergenic protein wherein the fragment consists of at least eight consecutive amino acids of the respective allergenic protein. Page 3, ¶ 2.

When fragments of allergenic proteins are employed it is possible to prepare a hybrid polypeptide comprising only fragments which have an allergenic activity which is lower compared with the respective allergenic proteins from which they are derived. This effect may be due to the destruction of epitopes by modified secondary or tertiary structure of the fragment compared with the full length protein. Page 3, ¶ 3.

Further, regarding the determination of the allergenic activity of the hybrid polypeptides, the invention teaches that "the allergenic activity of a sample is determined by determining the IgE antibodies which are induced in a test animal upon application of the sample. Page 3, ¶ 4.

Regarding modifications of the hybrid polypeptides, the invention teaches that:

The hybrid polypeptide of the invention does not necessarily consist only of amino acid sequences derived from allergenic proteins. It is possible that artificial sequences (e.g. spacer sequences) are inserted between the units representing sequences from different allergenic proteins. It is also possible that the amino acid sequences of the naturally occurring allergenic proteins are modified, e.g. by genetic engineering to introduce mutations which reduce the allergenic activity of the fragment. It is also preferred that the hybrid polypeptide comprises a "tag" sequence which facilitates the purification of the hybrid polypeptide upon expression in a host cell. Page 4, ¶ 2.

Regarding polynucleotides coding for the hybrid polypeptides, the invention teaches:

The invention further concerns a polynucleotide encoding a hybrid polypeptide according to the invention. Due to the degeneracy of the genetic code many different polynucleotide molecules may encode a single polypeptide. The polynucleotide of the invention preferably is an

expression construct for obtaining the polypeptide after expression in host cells. Page 4, ¶ 5.

Regard specific exemplification of the methodology of the present invention, Purified timothy grass pollen allergens were used. Applicants presented three tables and and seven figures demonstrating among other things:

1. That blood pre-sensitized with hybrid allergens are infective at inhibiting IgE binding to the constituent wild-type allergens (Table 1);

2. That blood pre-sensitized with hybrid allergens comprising unrelated allergens are effective at inhibiting IgE binding to the constituent wild-type allergens (Table 2);

3. That hybrid allergens will co-sensitize patients against sensitivity to their constituent wild type allergens (Figure 1);

4. That recombinant hybrid allergens induce stronger IgG_1 antibody response in mice than the individual components or mixtures thereof (Figures 5 and 7);

In terms of how to construct hybrid vaccines, Figure 2 clearly exemplifies one method of doing that although it by no means precludes using of other methods well known in the art. In Figure 2, the fusion of two genes (e.g. Phl p5, Phl p1) was mediated by a two-step PCT reaction, creating overlapping ends in the first PCR reaction followed by the amplification of both sequences in a second PCR step.

The Examiner's attention is particularly drawn to Example 2, starting from page 11 of the specification dealing with the construction of recombinant hybrid allergens. In one of the many teachings of the Application regarding how to construct hybrid allergens, Applicants taught:

> The cDNAs of Phl p 5 and Phl p 1 were obtained by polymerase chain reaction using the primers ... The signal peptide of Phl p 5 was replaced by a NdeI restriction site, containing the ATG start codon at the 5`end of the coding region. A KpnI restriction site was introduced at the 3`end of Phl p 5 replacing the stop-codon. The Phl p 1 sequence, lacking the signal peptide, started with a KpnI restriction site at the 5`end. At the 3`end a nucleotide stretch coding for a Hexahistidine-tag was introduced,

followed by a stop codon and a BamHI restriction site. The PCR products were inserted as NdeI/KpnI/BamHI fragment into a pET17b expression vector. Page 12, ¶ 3.

Applicants categorically assert that the introduction of a Hexahistidine-tag amounts to a modification of the hybrid polypeptide. Further, in light of what is already well known in the art, the restriction and ligation of cDNAs in order to create fragments of the hybrid polypeptide or indeed the insertion of sequences such as the above exemplified Hexahistidine-tag in order to otherwise modify hybrid polypeptides are adequately described in the Application and to burden the specification with well-known techniques in biotechnology is beyond the requirement of the law. Therefore, the Examiner's assertion that "there is no conception of a method for preparing a hybrid polypeptide comprising fragments thereof as claimed at the time of filing" is without basis as is shown above.

Furthermore, the Examiner asserts that Applicants have not taught what fragments will encode polynucleotides which are capable of encoding the polypeptide and that there is no teaching of a representative fragment. Applicants contend that written description may be satisfied through disclosure of relevant identifying characteristics, i.e. structure, other physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Again, what is well known to one of skill in the art need not be disclosed. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.

Fragments of known allergens can encompass an infinite permutation of polypeptides and to require the Applicants to particularize those fragments does not take due cognizance of what Applicants claim to have invented. Whereas Applicants are claiming hybrid polypeptides comprising allergens, insubstantial modifications of those hybrid polypeptides, whether by fragmenting them or otherwise, even at the level of one amino acid substitution or deletion or for that matter, the insertion of unnatural amino

acids so touch upon and infringe their invention that it is proper to claim the full scope of their invention.

Furthermore, were an artisan so inclined, they could seek to characterize fragments by amino acid or gene sequencing and even ascertain their full repertoire of T-cell or B cell epitopes using antibodies of predefined specificity. (See page 14, paragraph 5), but the inventors do not care so much about the structure of those fragments as they care that the fragments must contain at least eight consecutive amino acids from the native protein; that the fragments as part of the hybrid polypeptide must induce production of protective antibodies and finally, that as part of the hybrid polypeptide, that the fragments must have reduced allergenicity compared with the native protein. Applicants claim no more and no less and one of skill in the art will understand the inventors to be in possession of fragments and modifications of hybrid polypeptides having these characteristics at the time of filing of this invention.

In a Rule 132 declaration submitted prior, Dr. Rudolf Valenta attested to the fact that at the time the invention was made, the polynucleotide and polypeptide sequences for the timothy grass pollen allergens were available in the art. Also, at the time the invention was made, the primary structure of many allergens have been identified. As evident from the Exhibits attached to the said declaration, Phl p1 was disclosed in the Peterson, *et al.* reference in 1995, Phl p2 was disclosed in an article authored by Dr. Valenta in 1993, Phl p5 was disclosed in an article authored by Dr. Valenta in 1993, and Phl p6 was disclosed in an article authored by Dr. Valenta in 1999.

In view of the aforementioned remarks, Applicants respectfully request reconsideration of this rejection and withdrawal of this ground for rejection and all such other grounds based on inadequate description of fragments of the claimed hybrid polypeptides.

Rejection under 35 U.S.C. § 112, 1st paragraph – Claims 1-6, 13-15, 20-21 and 26

Claims 1-6, 13-15, 20-21 and 26 stand rejected under 35 U.S.C. §112, 1st paragraph, as failing to comply with the written description requirement. The Examiner asserts that the claims drawn to the fragments thereof, wherein the fragments consist of amino acid sequences that fail to recite any associate function and that it is unclear how to define fragments thereof with respect to what amino acids must be comprised therein to acquire the appropriate fragments. Therefore, the Examiner asserts that the claims lack an adequate description of both the fragments thereof and the function of the polypeptide.

Applicants respectfully traverse this rejection. As currently amended, none of the cited claims above have fragments of hybrid polypeptides as an element and this ground for rejection is now moot. As such, it withdrawal is kindly requested.

However, regarding claims 27 to 35, related to fragments and or modifications of hybrid polypeptides of the present invention, Applicants herein incorporate the aforementioned remarks in regards to the traversal of 112, first paragraph rejection of claims 13 and 14 as if it were set out herein in its entirety.

Applicants respectfully request reconsideration and withdrawal of this ground for rejection in view of the aforementioned remarks. In particular, the charge that the Applicants attempted to define the fragments by function alone does not accord with what the Applicants claims as their invention. In terms of function, these fragments must induce sufficient protective antibodies in vivo. In terms of characteristics, all that is required is not that they possess any particular sequence or particular epitopic profile, but that they merely comprise at least eight consecutive amino acids of the wild-type protein while have tolerable to low, if not non-existent allergenicity (IgE binding), so long as they induce protective antibody production (IgG production). Applicants submit that the pending claims satisfy the written description requirement and respectfully request that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. § 103 (a)

Claims 1-3 and 13-14 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al., (1996, J. Allergy Clin. Immun. Vol. 97(3):781-787).

The Examiner asserts that Ball et al. teach the major grass pollen allergen Phl p1. The Examiner asserts that Ball et al., while teaching that the Phl p1 can be part of a hybrid or fusion polypeptide does not specifically recite using another plant allergenic protein within the hybrid polypeptide. Vrtala et al. teach grass pollen allergens that can be expressed in prokaryotes.

Applicants assert that Ball and Vrtala et al. are not combinable in the sense that there is no motivation or suggestion to combine them in the manner which the Examiner asserts. Neither or these references alone or in combination teach that a fusion protein comprising grass allergens will have lower antigenicity than their constituent allergens. As such, there is no basis to combine them in the manner which the Examiner now deems obvious.

Further, the fusion proteins disclosed in Ball et al. are different from the polypeptides of the present invention. The fusion part like beta-galactosidase, GST or lambda cII protein are derived from the vector and serve purely for the expression of the fusion protein. Ball et al. does not teach nor suggest that the fusion polypeptide can be used as such for therapy, let alone immunotherapy of Type I allergic reactions.

Furthermore, neither Ball nor Vrtala mentions the concept of induction of protective antibodies which is the therapeutic target of the current invention. As such, the combination of Ball and Vrtala does not in any way render the claims of the instant Application obvious. It is respectfully requested that this ground for rejection be withdrawn.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office action and, as such, the present application is in condition for allowance. Applicants wish to expedite the prosecution process and if the Examiner believes, for any reason that personal communication will help expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

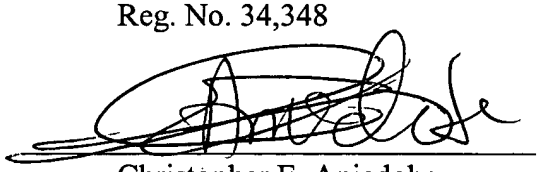
Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,

REED SMITH, LLP

By:_____

Toni-Junell Herbert
Reg. No. 34,348



Christopher E. Aniedobe
Reg. No. 48,293

Date: 09/25/2005

1301 K Street, N.W.
Suite 1100-East Tower
Washington, D.C. 20005
(202) 414-9200